Thermophysical properties of lidocaine:thymol or l-menthol eutectic mixtures

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\textbf{ABSTRACT}

\textbf{Backgrounds:} A key objective of green chemistry is to obtain a broad database of thermophysical properties of liquid mixtures. Thus, the replacement of conventional solvents with ecological ones will be facilitated.

\textbf{Methods:} Herein, two eutectic systems with therapeutic properties are characterized. They are binary mixtures of lidocaine and thymol or l-menthol. Properties as solid-liquid equilibrium, density, speed of sound, refractive index, isobaric molar heat capacity, surface tension, and viscosity were determined at 0.1 MPa and several temperatures. From them, others derivatives were calculated. In addition, the phase diagram was correlated with NRTL model and the density and isobaric molar heat capacity were modelled with PC-SAFT equation of state.

\textbf{Significant findings:} Although the mixtures with l-menthol were almost ideal, a complex diagram owing the presence of stable and metastable phases. For these mixtures, the values of all measured properties were lower than those with thymol. Results indicated that PC-SAFT can be used to predict the thermodynamic behaviour of both systems in any working condition.

\section{1. Introduction}

Solvents are probably the most active research field in the green chemistry [1]. Its presence is essential both in chemical reactions and in processes of separation and purification of compounds. Traditional solvents are water and the volatile organic compounds (VOCs). The first has great advantages but its polarity and reactivity with many solutes are great drawbacks [2]. The VOCs are very effective but are not sustainable [3]. Therefore, the replacement of VOCs by eco-friendly solvents is the focus in many industries that seek to more sustainable processes. Several alternatives as sCO\textsubscript{2}, ionic liquids, and biomass-derived solvents have been proposed [4]. Eutectic solvents are the most recent neoteric solvents. They are mixtures (no pure compounds or pseudo-compounds) so it should be noted that their preparation is easy, efficient and does not produce waste. Although the term eutectic is old, the rise of these systems has occurred in the last 20 years. Fredrick Guthrie coined it in 1884 and defined it as "a lower temperature of liquefaction than that given by any other proportion" [5]. In 2004, Abbott et al. [6] studied ChCl/carboxylic acids mixtures and introduced the acronym corresponding to deep eutectic solvent (DES). Currently, DESs are classified into five categories [7,8]. The first four have the general formula Cat \( X \) zY and the fifth are eutectic mixtures containing non-ionic compounds. Depending on the nature of its components, other acronyms are used. Literature collects interesting reviews on characteristics, types, properties, and applications of these mixtures [9–19]. In this paper, binary eutectic systems of type V containing active pharmacetical ingredients (APIs) are studied. They have therapeutic properties so are called THEDESs [20].

Specifically, the APIs used here are lidocaine (L) and thymol (T) and l-menthol (M). Lidocaine (2-(diethylamino)-N-(2,6-dimethylfenil)acet-amida) is a monocarboxylic acid amide prepared from the condensation of N,N-diethylglycine with 2,6-dimethylaniline. It was the first amine-amide local anesthetic, discovered in 1946 and marketed in 1949 [21, 22]. It is mainly used by dentists. In addition, L has the ability to block sodium channels and obstruct nerve signals, making it an effective antiarrhythmic and antiepileptic drug [21]. All this, together with its varied use as a surface anesthetic, makes its need in the market very important. It has been estimated at USD 1.19 billion by 2030 [23]. Lidocaine is present in a wide variety of formulations (injections, creams, gels, and inhalers for intubated patients) along with other active

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ingredients that enhance its effects. The best known is the eutectic mixture lidocaine-prilocaine sold as Emla®, Thymol (2-Iso-
propil-5-metilfenol) and l-menthol (2-isopropil-5-metilciclohexanol) are two terpenes that can be biosynthesized or extracted from plants. Both have biological activity and are known permeability enhancers [24–26]. They are Generally Recognized As Safe (GRAS) compounds according to the U.S Food & Drug Administration (FDA) classification [27]. The T and M structures differ only in the ring type; aromatic in the first and cyclic in the latter. This difference causes notable changes in the properties of their mixtures.

Several applications of the binary mixtures of L and T or M have been proposed as drug formulation, membranes development, and liquid-liquid extractions from aqueous solutions [28–35]. Despite this, these systems have been scarcely studied. An analysis of the structures by molecular dynamics was published by Abbas et al. [36,37]. Literature reports solid-liquid equilibria (SLE) data of both systems [30,38]. No more data were found. The lack of experimental data on physicochemical properties is a serious problem for the definitive replacement of VOCs and the improvement of the sustainability of the processes [12,14]. Tools such as the program for assisting the replacement of industrial solvents (PARIS III) [46] and the sustainable solvent selection and substitution software (SUSSOL) [47] provide the optimal substitute solvent for each process. This requires an extensive database of properties (density, phase equilibrium, refractive index, surface tension, heat capacity, viscosity, Hansen’s parameters, solubility in water or partition coefficients). They are also necessary to apply thermodynamic models. It is unusual to find papers including both the experimental determination and modelling of a large number of properties for these solvents. We aim to fill this gap in the knowledge.

The purpose of this work is to characterize lidocaine and thymol or l-menthol eutectic mixtures of compositions (1:1) and (1:2) in mole ratio. Data of solid-liquid equilibrium (SLE) and six thermophysical properties were measured and discussed. The effects of the temperature and composition on the properties were analysed and derived properties were calculated. Correlations between surface tension and critical temperature, or refractive index or viscosity were used. In addition, the validation of the perturbed chain-statistical associating fluid theory (PC-SAFT) equation of state (EoS) was performed for both systems to expand their use in the industry.

2. Experimental

2.1. Materials

The structures and characteristics of the pure compounds (L, T and M) are reported in Table 1. All of them were solid to 293 K. They were provided by Sigma–Aldrich and no purification processes were applied. The mixtures were prepared weighing each compound in adequate ratios with a PB210S Sartorius balance. The standard uncertainty was 1–10–7 g. After, stirring and light heating (323 K) was applied until a homogeneous liquid was obtained.

The acronym, composition, molar mass and melting temperature of each THEDES studied are reported in Table 2. A Karl Fisher method (automatic titrator Crison RF 15-2B) was used to determine the water content in the mixtures and a maximum value of 300 ppm was obtained.

2.2. Solid-Liquid equilibria

A differential scanning calorimeter (TA Instruments DSC Q2000) with an RCS refrigeration system was used to determine the solid-liquid equilibrium (SLE). Indium was used as standard to calibrate the temperature and heat flow and the calculated uncertainty was u(Tm) = 0.5 K. A liquid sample of 5 to 15 mg was weighed out and placed in an aluminium pan. For solid mixtures, it was preheated at a temperature above Tm to sure the crystallization into the device. After, the samples were cooled to 213–223 K at 3 K/min and then heated at the same scanning speed until 10 K above Tm. This scan rate was chosen regarding our previous studies.

Table 1
Chemicals used in this work.

<table>
<thead>
<tr>
<th>Chemical (Acronym)</th>
<th>CAS No</th>
<th>Source</th>
<th>Purity a</th>
<th>M / g mol⁻¹</th>
<th>Tm / K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (L)</td>
<td>137–58–6</td>
<td>Sigma-Aldrich</td>
<td>&gt;0.98</td>
<td>234.34</td>
<td>340.8/340.7 b</td>
</tr>
<tr>
<td>Thymol (T)</td>
<td>89–83–8</td>
<td>Sigma-Aldrich</td>
<td>&gt;0.985</td>
<td>150.22</td>
<td>322.5 c</td>
</tr>
<tr>
<td>L-Menthol (M)</td>
<td>89–78–1</td>
<td>Sigma-Aldrich</td>
<td>&gt;0.99</td>
<td>156.27</td>
<td>315.1 d</td>
</tr>
</tbody>
</table>

a As stated by the supplier (mass fraction);
b [48];
c Ref. [49];
d Ref. [50].
method used. In relation to LT system, no thermal events were observed in the thermograms; An example is shown in Fig. S1a. In the literature few points have been reported and they correspond to compositions at the extremes of the diagram [30,33,39]. For LM, complex thermograms (Figs. 1a and S1b and c) were obtained owing to the presence of both stable and metastable SLE diagrams. The stable diagram is related to the presence of a co crys tals of equimolar composition, firstly reported by Corvis et al. [40]. When co crys tals are not formed, metastable SLE diagrams were found. Owing to the polymorphism exhibited by M and studied by us in a previous work [55] two different liquidus curves were obtained. As Corvis et al. [40] stated, in situ recrystallized samples lead to β metastable phase diagram. Therefore, in our case, we should observe thermal transitions related to β metastable, however we have identified thermal transitions of both stable and metastable phase diagrams (Fig. 1b). At rich M compositions, liquidus and eutectic points of α and β metastable phases were obtained. The one identified as α – phase had Tm higher than β – phase. At compositions close to equimolar composition, metastable mixtures transform to stable ones showing exothermic peaks at 280–290 K. Once metastable eutectic phases melt, they reform the stable system. At rich L compositions, the same liquidus curves were detected for α and β phases. Based on the experimental values, the NRTL model [56] was applied to LM system. The equations are reported in the supplementary file and the parameters are in Table S1. Our data (Table 2, Fig. 1b) agreed with those published by Corvis et al. [40]. The LM mixtures exhibited almost ideal behaviour. A metastable state with two phases was detected. The one identified as α – phase had Tm higher than β – phase. The eutectic points obtained from NRTL model were: TmLα=283.07 K and xLα,eu=0.39; TmLβ=272.88 K and xLβ,eu=0.35. The experimental values of TmLα were higher than the ones reported by Corvis et al. [40]. This fact is logical because we take the maximum peak as Tm instead of onset temperature. In addition, two eutectic points related to stable SLE diagram were observed: TmL11=300.02 K at xL<0.5, and TmLu2=309.84 K at xL>0.5. For comparison, in Fig. 2b are included the eutectic and invariant points from literature [40].

### 2.3. Thermophysical properties

The devices used for thermophysical characterization of the studied mixtures are well-known and widely described in the bibliography. Table 3 collects the standard uncertainty in the temperature (u(T)) and the calculated combined expanded uncertainties for each property (U(Y)). Each apparatus was checked with benzene and the mean relative deviations (MRD(Y)) obtained by comparison between our data and those from literature are listed in Table 3 [53,54]. It was assumed that the equilibrium state was reached when the property measure was stable. For each property, tabulated data were the average of two replicates. In all cases, the coefficient of variation had to be lower than the experimental uncertainty.

### 3. Results and discussion

#### 3.1. Solid-Liquid equilibria

Knowing the solid-liquid phase diagram (SLE) of a solvent is essential for its implementation in any industrial application. It provides information about the stability of the solid and liquid phases as a function of temperature and composition. Additionally, in the case of eutectic mixtures, these diagrams can help to understand the physicochemical properties that characterize them. Also, the obtention of SLE phase diagram is the unique tool to distinguish a eutectic solvent from a deep eutectic solvent. In this work, when it has been possible, our experimental data have been compared to reported data to identify the detected thermal events and to analyze how can affect the experimental

<table>
<thead>
<tr>
<th>Property</th>
<th>Devices</th>
<th>u(T)/k</th>
<th>U(Y)/%</th>
<th>MRD(Y)/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ρ</td>
<td>Oscillating U-tube density meter, Anton Paar DSA 500°</td>
<td>0.005</td>
<td>0.05</td>
<td>0.004</td>
</tr>
<tr>
<td>u</td>
<td>Sing-around technique in a fixed-path interferometer, Anton Paar DSA 500°</td>
<td>0.005</td>
<td>0.5</td>
<td>0.026</td>
</tr>
<tr>
<td>nD</td>
<td>Standard Abbe refractometer, AbbeMet-HP refractometer Dr. Kernchen</td>
<td>0.01</td>
<td>2 10^-5</td>
<td>0.007</td>
</tr>
<tr>
<td>cP,in</td>
<td>Differential scanning calorimeter, TA Instruments DSC Q2000</td>
<td>0.5</td>
<td>1 %</td>
<td>0.028</td>
</tr>
<tr>
<td>γ</td>
<td>Drop volume tensiometer, Lauda TVT 2°</td>
<td>0.01</td>
<td>1 %</td>
<td>0.21</td>
</tr>
<tr>
<td>ν</td>
<td>Capillary viscometer Ubbelohde, Schott-Geräte AVS-440</td>
<td>0.01</td>
<td>1 %</td>
<td>0.28</td>
</tr>
</tbody>
</table>

a k = 2(0.95 level of confidence).

<table>
<thead>
<tr>
<th>MRD(Y) = 100 ∑</th>
<th>Yi - Yi,exp</th>
<th>Yi,exp</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>i=1</td>
<td>Yi - Yi,exp</td>
<td>Yi,exp</td>
<td>100</td>
</tr>
</tbody>
</table>

Calibrated with two reference fluids: air and water MilliQ (resistivity of 18.2 μS cm⁻¹).

Calibrated with water MilliQ (resistivity of 18.2 μS cm⁻¹) as reference fluid.

6 cycles of 6 drops per cycle were averaged.
density values of fluids at any composition and temperature is essential for its implementation in the industry. To this end, equations of state (EoS) such as PC-SAFT have been postulated as effective tools but must be previously validated. A brief summary of this model developed by Gross and Sadowski [57, 58] is found in the supplementary file. In this EoS, each pure associated compound is characterized by five parameters for its implementation in the industry. To this end, equations of state (EoS) such as PC-SAFT have been postulated as effective tools but must be previously validated. A brief summary of this model developed by Gross and Sadowski [57, 58] is found in the supplementary file. In this EoS, each pure associated compound is characterized by five parameters.

For L, association parameters were taken from the literature and the rest were rescaled to fit its boiling point published by Martins et al. [52]. For L, association parameters were taken from the literature and the rest were rescaled to fit its boiling point published by Martins et al. [52]. For L, association parameters were taken from the literature and the rest were rescaled to fit its boiling point. The new parameters were validated by comparing the predicted one. The parameters and deviations are collected in Table 5. In the modelled of mixtures, mixing rules with a binary interaction parameter (k_L) are included. In our study, we have taken k_L=0. Therefore, the model was used in its predictive version. To validate the PC-SAFT EoS for all THEDEs, our experimental ρ values were compared with those predicted ones. The mean relative deviations were MRD(ρ)=0.35 % and 0.11 % for LT11 and LT12, and MRD(ρ)=0.76 % and 0.49 % for LM11 and LM12. Overall, the model slightly overestimated ρ to a greater extent for the mixtures with M (Fig. S2a). The low deviations did not justify the introduction of a parameter k_L≠0.

The variation of ρ with T was linear as expected in most liquids systems (Fig. 2a) and the coefficients are listed in Table 6. The isobaric expansivity (α_ρ), calculated with the following equation [60], allows quantifying the effect of T on ρ:

\[
α_ρ = \frac{1}{ρ} \frac{∂ρ}{∂T}
\]  

(1)

The α_ρ values at 298.15 K are reported in Table 4 and displayed at several temperatures in Fig. S3a. They were higher for LM system and increased with the terpene mole fraction. A comparison with similar mixtures of T and M with other compounds such as carboxylic acids is possible [49,50]. The mixtures studied here were denser and had higher expansion capacity than those. This fact could indicate strong terpenes-L interactions.

The more compact a material is the faster sound propagates through it. So, the u values of a fluid are related to its compaction. For the mixtures with T, they were about 50 m/s higher than those with M (Table S3). This property slightly increased with x_L in both systems and markedly decreased with T (Fig. 2b). The coefficients of the u − T linear correlations are given in Table 6. The isentropic compressibility (κ_s) is calculated from ρ and u data at each T. Subsequently, the free intermolecular length (L_f) can be estimated using the constant of Jacobson (K) [61]:

\[
L_f = K/κ_s = (91.368 + 0.3565T)10^{-8} \left(\frac{1}{ρu^2}\right)
\]  

(2)

Table 4 collects κ_s and L_f data at 298.15 K. According to the above results, both properties were lower for the mixtures with T and decreased, very slightly for LT system, with x_L increasing. The L_f increased with T (Fig. S3b) due to the increase in the thermal agitation. The temperature coefficient for this property was similar for the four mixtures and the value was (10 L_f/∂T) = 2·10^{-3} Å·K^{-1}.

The n_2 values of LT system were significantly higher than those for LM (Table S4). For the first, the effect of the composition on n_2 was negligible. Also, a linear correlation with T was found for all cases as can be seen in Fig. 2c and Table 6. The molar refraction (R_m), a property related to polarizability, can be calculated with the Lorentz-Lorentz equation [60]:

\[
R_m = \left(\frac{n_2^2 - 1}{n_2^2 + 2}\right)V_m
\]  

(3)

Where V_m is the molar volume of the fluid at same ρ and T. Unlike n_D, the effect of the L ratio on R_m was stronger than the effect of terpene type (Table 4 and Fig. S3c). Thus, mixtures with a similar mole ratio presented similar R_m values and they were higher for the equimolar ones. Concerning similar mixtures with carboxylic acids previously published [49,50], the systems studied here exhibited an R_m up to 20 % higher than those. The aromaticity of the L molecule and the free electrons of the amine and amide groups would justify this result. The (V_m − R_m) difference is an estimation of the free volume (V_u) of the system. The f_n values at 298.15 K were 69.5 % for both LT mixtures, and 70.9 % and 71.5 % for LM11 and LM12, respectively.

The measured G_p,m data of LM system were 8.5 % to 10 % higher than those of the LT in accordance with the higher molar mass of the former (Table S5). They ranged from 325 J·mol^{-1}·K^{-1} of LT12 at 278.15 K to 429 J·mol^{-1}·K^{-1} of LM11 at 338.15 K. The higher the temperature, the more energy the fluids store. Thus, the slope of G_p,m − T correlation must be positive as Fig. 2d shows. This property was also modelled with PC-SAFT EoS. The values were well predicted, especially those of the
THEDES with T. The average deviations were MRD($C_{p,m}$) = 1.5 % for LT and 6.0 % for LM mixtures. A graphical comparison can be found in Fig. S2b.

Surface properties is related to the strength of the interactions within the fluid. Intermolecular forces must be weakened to increase the number of molecules at the fluid-air interface. The values of our systems were in agreement with the results from the above properties in which the L-T interactions were stronger than L-M (Table S6). For the first, $\gamma$ was 10% higher than for the latter. The effect of $T$ on $\gamma$ was similar in both systems showing a linear correlation (Fig. 2c and Table 6). From $\gamma$ – $T$ data, thermodynamic properties such as the entropy of surface ($\Delta S_S$) and enthalpy of surface ($\Delta H_S$) can be calculated [60]:

$$\Delta S_S = -\frac{\partial \gamma}{\partial T}$$

$$\Delta H_S = \gamma - T\left(\frac{\partial \gamma}{\partial T}\right)$$

The higher the value of these properties, the more structured the fluid is. The calculated data indicated a high structuration within the mixtures with T (Table 4). Inside the liquid, the molecule is subjected to a symmetrical force field. Upon moving to the interface, the symmetry disappears and the molecule becomes polarized. The $\gamma$ can be considered a consequence of this lack of symmetry and therefore, a measure of the polarization of molecules in the liquid surface. So, there is a correlation [62] between $\gamma$ and the dielectric constant or $n_D$ for liquids without strong hydrogen bonds (supplementary file). Table S8 reports the adjustment coefficients and shows high linearity with regression coefficients greater than 0.995. Considering that $\gamma$ must be zero at the critical temperature ($T_c$), different authors have proposed correlations.

![Fig. 2. Experimental thermophysical properties of THEDESs studied at several temperatures and at $p = 0.1$ MPa. (a), density, $\rho$; (b) speed of sound, $u$; (c) refractive index, $n_D$; (d) isobaric molar heat capacity, $C_{p,m}$; (e) surface tension, $\gamma$; (f) dynamic viscosity, $\eta$. (●), LT11; (■), LT12; (○), LM11; (□), LM12. Points, experimental values; (–), correlated data; (—–), PC-SAFT EoS LT system; (– – –) PC-SAFT EoS LM system.](image)
and PC-SAFT allow estimating the critical temperatures and pressures (Table 4).

Table 4
Experimental and calculated properties of THEDESs studied at T=298.15 K and p = 0.1 MPa.

<table>
<thead>
<tr>
<th>Property</th>
<th>LT11</th>
<th>LT12</th>
<th>LM11</th>
<th>LM12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ρ/ kg m⁻³</td>
<td>989.66</td>
<td>989.64</td>
<td>953.20</td>
<td>935.71</td>
</tr>
<tr>
<td>u/ m s⁻²</td>
<td>1459.97</td>
<td>1454.74</td>
<td>1412.18</td>
<td>1402.15</td>
</tr>
<tr>
<td>Tc</td>
<td>1.52149</td>
<td>1.52004</td>
<td>1.49306</td>
<td>1.48274</td>
</tr>
<tr>
<td>g_c / mol⁻¹ K⁻¹</td>
<td>366</td>
<td>337</td>
<td>396</td>
<td>367</td>
</tr>
<tr>
<td>γ/ mN m⁻²</td>
<td>33.84</td>
<td>33.14</td>
<td>30.96</td>
<td>30.05</td>
</tr>
<tr>
<td>ν/ mPas</td>
<td>114.33/111.3</td>
<td>79.49/99.3</td>
<td>46.06</td>
<td>46.20/45.91/</td>
</tr>
<tr>
<td>η/ mPas</td>
<td>177.15</td>
<td>0.746</td>
<td>0.763</td>
<td>0.767</td>
</tr>
<tr>
<td>α_a/kK⁻¹</td>
<td>474.05</td>
<td>479.46</td>
<td>526.06</td>
<td>543.59</td>
</tr>
<tr>
<td>L_a/Å</td>
<td>0.430</td>
<td>0.433</td>
<td>0.453</td>
<td>0.461</td>
</tr>
<tr>
<td>D_a/Å⁻¹ m⁻³ mol⁻¹</td>
<td>59.21</td>
<td>54.62</td>
<td>59.55</td>
<td>55.61</td>
</tr>
<tr>
<td>∆S_a/ mJ m⁻³ K⁻¹</td>
<td>0.091</td>
<td>0.084</td>
<td>0.081</td>
<td>0.080</td>
</tr>
<tr>
<td>∆H_a/ mJ m⁻³</td>
<td>60.97</td>
<td>58.18</td>
<td>55.17</td>
<td>53.87</td>
</tr>
<tr>
<td>ρB / kJ mol⁻¹</td>
<td>63.96/67.67</td>
<td>62.30/62.5</td>
<td>54.87</td>
<td>58.52/60.01</td>
</tr>
</tbody>
</table>

* Standard uncertainties are: u(T)=0.005 K for ρ and u, 0.5 K for C_p,m, and 0.01 K for the rest of properties. The combined expanded uncertainties (0.95 level of confidence, k=2) are U(L_a)=0.05 kg m⁻³; U(L_c)=0.5 m s⁻¹; U(L_h)=2.10⁻¹ kg; U(C_p,m)=30% (U(C_p,m)=1%; U(Tc)=1%; U(η_a)=0.04 kK⁻¹; U(η_a)=0.22 TPa⁻¹; U(U)=0.005 Å; U(L_a)=0.004 cm⁻³ mol⁻¹; U(∆S_a)=0.001 mJ m⁻³ K⁻¹; U(∆H_a)=0.06 mJ m⁻³.

† Ref. [43].
‡ Ref. [45].
* Ref. [42].

Table 5
PC-SAFT parameters used to model the studied THEDESs. The type 2B (one donor and one acceptor site) was considered as association scheme.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m</th>
<th>ε/Å</th>
<th>C/ K</th>
<th>x₁,R</th>
<th>x₂,R</th>
<th>MRD(T13)/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymol</td>
<td>4.012</td>
<td>3.816</td>
<td>290.22</td>
<td>0.0616</td>
<td>1660.0</td>
<td>0.4†</td>
</tr>
<tr>
<td>Menthol</td>
<td>4.152</td>
<td>3.903</td>
<td>262.40</td>
<td>0.0996</td>
<td>1785.6</td>
<td>0.3‡</td>
</tr>
<tr>
<td>Lidoacine</td>
<td>6.320</td>
<td>3.770</td>
<td>285.85</td>
<td>0.01</td>
<td>2798.5</td>
<td>0.5§</td>
</tr>
</tbody>
</table>

* Ref. [52].
† Ref. [59].
‡ This work.
§ Ref. [48].

between both properties. Herein, we used the Guggenheim [63] and Eötvös [64] equations (supplementary file). In addition, EoSs as PC-SAFT allow estimating the critical temperatures and pressures (Tc and p_c) of the systems. Although this model tends to overestimate the critical properties of the compounds, in our case the deviation of Tc of pure M was small (2.7 K). For T, it was higher (38 K) but the experimental value should be updated [49]. Furthermore, the thermodynamic properties of the mixtures were well predicted. The goodness of these results suggests that modelling of both critical loci could be acceptable. Table S9 lists the correlated and predicted values and Fig. 3 shows the critical loci.

The η indicates the ability of a system to flow. Table S7 reports the values measured in this work. Contrary to what is observed in other mixtures of these terpenes [49,50,55], the LT mixtures were more viscous than LM ones, especially at low T (Fig. 2f). For the first system, the η measured were very high and the values of the equimolar mixture were between 1.6 and 1.4 times higher than in the other. This ratio decreased with T increased. Increasing the x_l in the mixture increases the number of flatter molecules and decreases the number of I-T interactions. In consequence, the mobility of the fluid would be favoured. Also, the thermal agitation makes it difficult to maintain intermolecular interactions so the difference in fluidity of both mixtures is minimized at high T. On the other hand, the viscosities for both LM mixtures were similar and the variation of η with the terpene concentration at T lower than 298.15 K was opposite to that in the previous system. These results could be explained considering that, although the I-M interactions were weaker than I-T ones, the structure of menthol caused greater steric hindrance. In the literature, we have found published η data of LT11 and LM12 from 293.15 to 353.15 K [43]. The maximum deviations with our data were 3.03 and 0.29 mPas, respectively. Also, our η data of LT12 in the T range from 293.15 to 328.15 K were compared with those published by Dietz et al. [42]. The maximum deviation was of 7.5 mPas. Again, data at 298.15 K reported by van Osch et al. [45] were very higher than the others (Table 4). Regarding the influence of T on η, the experimental data of all mixtures were correlated following the VFT exponential equation. The equation and coefficients A_V, B_V, and C_V are given in Table 6. The first is related to steric hindrance owing represents the η at T → ∞. The others are used to calculate the activation energy for viscous flow (E_dη) [65]:

$$E_d\eta = R \left( \frac{\eta}{T} \right)^{\gamma}$$

The results were in agreement with the structures of the compounds and with the above results. Thus, A_V increased with x_l and was greater for the mixtures with M. Moreover, E_dη Values were higher in the mixtures with T, which shows that the I-T interactions were stronger than the I-M ones (Table 4, Fig. S3d). For LT system, the influence of T on E_dη was more pronounced in the equimolar mixture showing that the interactions in LT12 were lower. For LM, the effect was similar for both compositions.

Finally, the Pelofsky and Murerjee equations [66] correlate η and γ at similar p and T. The equations are found in the supplementary file and parameters are listed in Table S10. The obtained regression coefficients ranged from 0.90 to 0.95 for the former equation and 0.98 to 0.99 for the second.
were: maxima mean relative deviations concerning the experimental values respectively. Finally, PC-SAFT EoS was validated in both systems. The good linearity with regression coefficients higher than 0.99 and 0.90, respectively. Four therapeutic deep eutectic solvents (THEDESs) composed of lidocaine and thymol or l-menthol were studied. Melting temperatures and the following properties were determined at 0.1 MPa: density, speed of sound, refractive index, isobaric molar heat capacity, surface tension, and the viscosities showed good linearity with regression coefficients higher than 0.99 and 0.90, respectively. Finally, PC-SAFT EoS was validated in both systems. The maxima mean relative deviations concerning the experimental values were: \( \text{MRD}(\rho) = 0.8 \% \) and \( \text{MRD}(C_p, m) = 6 \% \)

4. Conclusions

Four therapeutic deep eutectic solvents (THEDESs) composed of lidocaine and thymol or l-menthol were studied. Melting temperatures and the following properties were determined at 0.1 MPa: density, speed of sound, refractive index, isobaric molar heat capacity, surface tension, and the viscosities showed good linearity with regression coefficients higher than 0.99 and 0.90, respectively. Finally, PC-SAFT EoS was validated in both systems. The maxima mean relative deviations concerning the experimental values were: \( \text{MRD}(\rho) = 0.8 \% \) and \( \text{MRD}(C_p, m) = 6 \% \)

CRediT authorship contribution statement


Data availability

All data generated or analysed in this study are included in the published article.

CRediT authorship contribution statement


Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtice.2024.105631.

References


Fig. 3. Critical loci predicted with PC-SAFT EoS vs lidocaine molar ratio, \( x_L \). (a) Critical temperature, \( T_c \); (b) Critical pressure, \( p_c \). (–) LT; (red), LM. ( ), pure M, ref. [48]; ( ), pure T, ref. [48].

8
